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Assistant Commissioner for Patents
U.S. Dept. of Commerce / Patent & Trademark Office
Attn: Examiner Dwayne C. Jones, AU 1614
Washington, D.C. 20231

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RE: Pat. Application #09/781,491
Clouatre, et al., Methods And Pharmaceutical Preparations For Normalizing Blood Pressure With (–)-Hydroxycitric Acid
Office Action of 10 February 2002, received 28 January 2002

Dear Mr. Jones:

My response to the Office Action of 28 January 2002 re Application #09/781,491 will follow the order of points made in that Action. My feeling is that distinctions need to be made as to what is actually being claimed in the prior art cited in that Action and the grounds for the claims made. Once the proper distinctions are in place, it will be quite clear that Dr. Dunn and I have presented a novel finding. However, inasmuch as we are both simply researchers and not patent agents nor attorneys, we may require some help in properly phrasing our claims as per MPEP § 707.07(j).

If we begin with the Office Action, page 2, paragraph 5, which is based upon U.S. Patent No. 6,221,901 B1 by Shrivastava, et al., it should be noted that this patent is making claims regarding magnesium for which (–)-hydroxycitric acid happens to be a ligand rather than for (–)-hydroxycitric acid *per se*. This characterization is important because quite literally all of the claims made by Shrivastava et al. are based upon known effects of magnesium itself. With regard to the particular issue at hand, it has been known for decades that magnesium has a hypotensive effect in many animal models and in humans. Shrivastava et al. break no new ground on this point. Moreover, to repeat, Shrivastava et al. do not claim that (–)-hydroxycitric acid itself reduces blood pressure. Had they known this, the authors would have said as much.

Similarly, Shrivastava et al. make no claims for any salt of (–)-hydroxycitric acid other than magnesium. Therefore it is quite clear that their patent claims are solely for magnesium with some supposed special merit arising from the use of (–)-hydroxycitric acid as a ligand. Here I leave aside the fact that no tests nor other evidence is presented to demonstrate that magnesium hydroxycitrate is superior in any way to the many other available salts of magnesium for the purposes of reducing blood pressure. Inasmuch as the benefits being put forth by Shrivastava et al. are classic for magnesium supplementation, one would legitimately have expected to be offered a demonstration of superiority in order to establish the novelty of the claims being made. In any case, what we find in Shrivastava et al. is a claim for the efficacy of magnesium for reducing blood pressure if (–)-hydroxycitric acid is the ligand.

Moreover, it should be noted that a known side effect of hypermagnesemia, i.e., excessive

magnesium levels, is a reduction in blood pressure. (Mordes JP, Wacker WE. Excess magnesium. Pharmacol Rev. 1977 Dec;29(4):273-300.) Shrivastava et al. maintain (column 8, lines 39-43) that the toxicity of magnesium hydroxycitrate is greater than 7 g/kg per os in the rat. It is not at all clear where this figure comes from when tests performed by Roche Pharmaceutical and published in peer reviewed journals indicate that a lethal dose for 50% of the animials ingesting (–)-hydroxycitric acid begins somewhere just on the other side of 4 g/kg. (Sullivan AC, Triscari J. Metabolic regulation as a control for lipid disorders. I. Influence of (–)-hydroxycitrate on experimentally induced obesity in the rodent. The American Journal of Clinical Nutrition May 1977;30, 5:767-776.) If by toxicity Shrivastava et al. mean death, their assertion may be accurate, but otherwise, it is misleading.

Using the standard 5:1 multiplier for rat to human data, the dose of magnesium hydroxycitrate employed by Shrivastava et al., i.e., 500 mg/kg/day, is equivalent to a human ingesting 100 mg/kg/day or 7 grams for the average-sized human subject. Of this amount, 45% would be elemental magnesium, hence we have the equivalent of a human ingesting approximately 3.15 grams of magnesium. The *Recommended Dietary Allowances*, 10th edition (National Research Council, 1989), indicates that most humans begin to suffer diarrhea at more than 350 mg/day. In other words, the test dose used by Shrivastava et al. is nearly 10 times the dose at which side effects would normally be expected to begin to appear. The diarrhea induced itself would lower blood pressure rapidly. Although it is true that with normal kidney function, great quantities of magnesium can be cleared from the system via the urine, the diarrhea induced by excessive magnesium ingestion is another matter entirely. Hence, any researcher in this field would immediately suspect that the data demonstrating blood pressure lowering supplied by Shrivastava et al. is indicative of magnesium toxicity — either hypermagnesemia or induced diarrhea — and not therapy. At this level of magnesium intake, there is no way of demonstrating any effect, one way or the other, for the ligand (–)-hydroxycitric acid. And, indeed, Shrivastava et al. do not attempt to demonstrate that the ligand is special, merely that magnesium hydroxycitrate causes a lowering of blood pressure when given in massive amounts.

Therefore, my responses to the first points of the Office Action are 1) Shrivastava et al. are making claims regarding magnesium with (–)-hydroxycitric acid as a ligand whereas Dr. Dunn and I are making claims regarding (–)-hydroxycitric acid *per se*, 2) the effects claimed by Shrivastava et al. are those of either hypermagnesemia or some other side effect induced by a massive dose of magnesium hydroxycitrate, and therefore are in no way supportive of the claims being made, and 3) the hypotensive effects of magnesium, especially at quasi-toxic intakes, have been known for decades. The claims which Dr. Dunn and I make for (–)-hydroxycitric acid *per se*, in contrast, are entirely novel.

The European Patent Application 803,202 A2 by Littera et al. suffers from defects similar in nature to those found with Shrivastava et al. At the very least, all three of the conditions mentioned on page 2, lines 7-12, (reducing obesity, blood lipids and hypertension) are known and long claimed effects of chromium alone. Preuss H, et al. in a study published two years before the Littera et al. application was filed show the blood pressure regulating effects of chromium. (Preuss HG, et al. Effects of chromium and guar on sugar-induced hypertension in rats. Clin Nephrol. 1995 Sep;44(3):170-7.) In fact, all the claims made by Littera et al. can be found in the

literature for chromium alone prior even to 1980. (McCarty MF. The therapeutic potential of glucose tolerance factor. Med Hypotheses. 1980 Nov;6(11):1177-89.) Where is there any novelty in making a hypotensive claim for a mixture of chromium with chitosan and (–)-hydroxycitric acid?
Where is there any indication that Littera et al. have even the slightest awareness that (–)-hydroxycitric acid by itself lowers elevated blood pressure? The answer to both of these questions is that there is none.

However, matters are far worse than a mere lack of novelty and a mere lack of any claim specific to (–)-hydroxycitric acid. Chitosan is a well-researched substance which has been repeatedly demonstrated to bind ionic compounds and minerals. This is a primary reason that it is used in water filtration systems. Littera et al.'s suggested delivery of (–)-hydroxycitric acid via preparation largely consisting of chitosan compromises all the known actions of (–)-hydroxycitric acid and is totally self-defeating as far as (–)-hydroxycitric acid is concerned. As can be shown from data from our studies, (–)-hydroxycitric acid is radically reduced in its absorption if allowed to bind onto gums, fibers and a number of other items because humans lack the ability to cleave (–)-hydroxycitric acid from these items in the gut. The result is that the entire complex is merely eliminated via the feces. Even the mineral most commonly used as a ligand for (–)-hydroxycitric acid -- calcium -- binds to (–)-hydroxycitric acid and then leads to saponification in the gut, and thereby to a dramatic reduction in uptake. Dr. Dunn and I indicate these problems in our pending Patent Application for the controlled delivery of (–)-hydroxycitric acid.

This point is brought home by a recent clinical trial and the exchanges in a medical journal regarding the results. Two of the three major US producers of (–)-hydroxycitric acid products for the health food market have used the problem of unwanted binding of (–)-hydroxycitric acid to fibers as an explanation for the poor showing of the compound in a major obesity trial. (Heymsfield, Steven B, et al. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent. JAMA 280, 18 (1998) 1596-1600; especially, Letters, JAMA 282 (1999) 235.) The chitosan proposed by Littera et al., of course, will act like a gum or fiber ligand to (–)-hydroxycitric acid. All of this has been confirmed by recent studies, to wit: Researchers at the University of California, Berkeley, found that absorption of (–)hydroxycitric acid in their particular model peaks 2 hours after administration and that the compound remains in the blood for more than 9 hours after ingestion. Eating a meal shortly after taking (–)-hydroxycitric acid reduces its absorption by about 60%. (Loe Y, Bergeron N, Phan J, Wen M, Lee J, Schwarz J-M, Time Course of Hydroxycitrate Clearance in Fasting and Fed Humans, FASEB Journal, 15 4:632, Abs. 501.1, 2001.) Littera et al.'s proposed formulation is tantamount to eating a small meal.

I argue, therefore, that Littera et al. demonstrates no knowledge of the physiological effects of (–)-hydroxycitric acid and shows no understanding whatsoever of its physical/chemical properties. Moreover, material readily available in the public domain is sufficient to cast doubt upon any loose claim that a combination product including chitosan might be an acceptable delivery vehicle for (–)-hydroxycitric acid.

Finally, there is the matter of Hastings et al., US Patent No. 5,626,849. Two points are made

in the Office Action. One is that (in column 4, lines 18-42) it is taught that (–)-hydroxycitric acid does not cause hypertension. However, this is a complete misreading of the meaning of this paragraph. To say that a compound does not cause a condition, of course, is in no way an indication that said compound might benefit that condition. Beyond that, the paragraph from Hastings et al. must be placed against the background of a marketplace in which ephedrine-based weight loss products are being sold. Ephedrine has a pressor effect, whereas (–)-hydroxycitric acid does not. This is all that can be extrapolated from the phrase indicated. Inasmuch as I am the ultimate author of the literature Hastings et al. list under "Other Publications" as Citrimax® Product Brochure, I am quite well aware of the material upon which Hastings et al. drew. (I authored nearly all of the (–)-hydroxycitric acid literature either produced or given away by the Interhealth Company in the period 1994-95, including the Technical Reference Guide and the booklet *The Diet and Health Benefits of HCA*, which Hastings et al., as Interhealth customers, would have been aware of in 1994 long before their patent application was filed.)

The other objection made in the Office Action, to wit, that increased levels of cholesterol can form plaques on the endothelium which would necessitate a compensatory increase in blood pressure is simply not accepted medically as a cause of hypertension. Some lay individuals may falsely believe this, but no one skilled in the art does. The literature review which I provided with the application does not list a single cholesterol lowering drug as being used for hypertension or as being of benefit in hypertension. Indeed, many hypotensive drugs actually worsen the blood lipids profile. (Preuss HG, Burris JF. Adverse metabolic effects of antihypertensive drugs. Implications for treatment. Drug Saf. 1996 Jun;14(6):355-64.) The primary causes of hypertension are fluid regulation and a failure of the smooth muscle of the endothelium to properly dilate or relax. Therefore, contrary to the objection, no one skilled in the art would make the extrapolation from Hastings et al. suggested in the Office Action.

In passing, I should note that the formulations proposed by Hastings et al. are backed by no evidence of efficacy. Having performed the animal trial myself with one of the arms being the Hastings et al. formulation, I can say with confidence that at the levels of intake asserted in that patent, the formulation performs no better than placebo. In part, this no doubt is related to the binding issue raised above in response to the objections based upon Littera et al. Inasmuch as disinterested third parties have now demonstrated that the problem is significant, I cannot be accused of special pleading in this matter.

I conclude, therefore, that there are no valid objections in the Office Action based upon Shrivastava et al., Littera et al. or Hastings et al. None of these show any awareness of the effects of (–)-hydroxycitric acid per se upon blood pressure and the latter two propose formulations which will actually negate the effects of (–)-hydroxycitric acid by reducing its uptake to a meaningless level.

Thank you for your time and efforts.

Sincerely,

Dallas L. Clouatre

Dallas L. Clouatre, Ph.D.